IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Muthukumaran Natarajan et al.	Examiner:	Sun Jae Loewe
Serial No.:	10/583,805	Group Art Unit:	1626
Filed:	June 22, 2006	Docket No.:	2867.002US1
Customer No.:	21186	Confirmation No.:	4884

Title: NOVEL STABLE POLYMORPHIC FORMS OF AN ANTICONVULSANT

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Dr. K. Srinivasu, declare and say as follows:

1 I am a citizen of India, and reside at Vadodara, Gujarat, India.

2. I joined SUN PHARMACEUTICAL INDUSTRIES LIMITED ("SUN") on May 27, 1999 and have been working in their R&D centre, in the Organic Synthesis Department, ever since. At present, I hold the position of Senior Manager-R&D (Organic synthesis), heading a group of 9 scientists in Organic Chemistry. Over the past 9 years at SUN, I acquired proficiency in conducting Process Research and development of complex active pharmaceutical ingredients (API's) of interest to the organization

3. I pursued my academics in India and Graduated (1991) in Chemistry from Nagarjuna University, Andhra Pradesh; Post Graduated (1993) in Organic Chemistry from Kakatiya University, Andhra Pradesh; and was awarded my Ph.D. (Chemistry) in 2001 from Kakatiya University, Andhra Pradesh.

4. I have reviewed and understand the above-identified application, the pending claims thereof, the pending Office Action, and references cited by the Examiner in the above-identified application. Specifically these references include Ahrndt et al, U.S. Patent 5,958,951, Andersen et al. (*J. Med. Chem.* **1993,** *36,* 1716-1725), and Gronvald et al. (U.S. Patent 5,010,090).

5. I am making the following statements as one of ordinary skill in the art in support of the patentability of the pending claims of U.S. Patent Application Serial No. 10/583,805.

6. In the Office Action mailed August 29, 2008, the Examiner rejected claims 1, 3 and 4 under 35 U.S.C. § 102(b) or in the alternative, under 35 U.S.C. 103(a) as allegedly being anticipated or obvious over Ahrndt et al, U.S. Patent 5,958,951. The disclosure of '951 patent can be considered to teach one anhydrous form. The anhydrous form is characterized by the XRD peaks at 6.4, 11.3, 13.0, 13.9, 15, 18.7, 19.4, 22.5 and 23.7

7. Under my direction, our laboratory prepared Tiagabine hydrochloride by following the process as disclosed in Examples 1 and 3 of U.S. Patent 5,958,951. When subjected to X-Ray diffraction, the XRD data of the samples revealed peaks similar to that disclosed in the XRD pattern of U.S. Patent 5,958,951. This data is shown in the Attached Exhibit I as XRD of Batch 7022/F/641/12 and in Exhibit II as 7022/F/641/13. Thus, it is quite clear that the polymorph obtained by following the process disclosed in the '951 patent (Examples 1 and 3), is indeed the polymorph as disclosed (XRD pattern) and claimed in '951 patent.

8. In addition, we prepared tiagabine hydrochloride following the procedure disclosed in U.S. Patent 5,354,760 (Petersen et al). It is my understanding that

this patent has been cited in the present application and a copy has been submitted to the Patent Office. The material prepared as disclosed in the '760 patent was dried at 80°C as disclosed in '951 patent (column 1, lines 31-35) and subjected to X-Ray diffraction. The XRD data for this sample is shown in the Attached Exhibit III as 7022/F/641/06E. The XRD data of the samples revealed peaks virtually identical to that disclosed in the XRD pattern of U.S. Patent 5,958,951.

9. Further, to establish that the Tiagabine hydrochloride polymorph as disclosed and claimed in '951 patent is different from the Tiagabine hydrochloride polymorph IV recited in the claims of U.S. Patent Application Serial No. 10/583,805, we are enclosing a letter from Professor T. N. Guru Row of the Solid State and Structural Chemistry Unit, Indian Institute of Science, Bangalore India. Professor Guru Row analyzed the sample 7022/F/641/06E of Tiagabine hydrochloride prepared in our laboratory according to the procedure disclosed above, and compared it with a sample of Tiagabine hydrochloride Polymorph IV prepared in our laboratory as disclosed and claimed in the present patent application, U.S. Patent Application Serial No. 10/583,805. As can be seen from Professor Guru Row's letter, the XRD patterns and crystal lattice cell parameters of the Tiagabine hydrochloride prepared as disclosed and claimed in the '951 patent are different from those claimed in U.S. Patent Application Serial No. 10/583,805. This clearly indicates that the Tiagabine hydrochloride, obtained as prepared and disclosed in the '951 patent, is different from the new and previously unknown Tiagabine hydrochloride Polymorph IV claimed in U.S. Patent Application Serial No. 10/583,805.

10. In the Office Action mailed August 29, 2008, the Examiner rejected claims 1-4 under 35 U.S.C. § 102(b) or in the alternative, under 35 U.S.C. 103(a) as allegedly being anticipated or obvious over Andersen et al. (*J. Med. Chem.* **1993**, *36*, 1716-1725). Under my direction, our laboratory studied the

recrystallization of Tiagabine hydrochloride from acetone by the procedure disclosed in Exhibit V.

11. Our study indicated that when Tiagabine hydrochloride was recrystallized from acetone, we obtained the material as solvate of acetone with an acetone content of 42149 ppm (i.e. tiagabine hydrochloride:acetone in a mole ratio of 1:0.34). The XRD pattern of this material, shown in the attached Exhibit VI as 7022/F/691/32B, is different from that of Tiagabine hydrochloride Polymorph IV. Thus, our observations are in accord with those disclosed in the '951 patent (column 1, lines 45-50).

12. In the Office Action mailed August 29, 2008, the Examiner rejected claims 1-4 under 35 U.S.C. § 102(b) or in the alternative, under 35 U.S.C. 103(a) as allegedly being anticipated or obvious over Gronvald et al. (U.S. Patent 5,010,090). Gronvald does not disclose the details of the process for recrystallizing Tiagabine hydrochloride from ethyl acetate. Under my direction, our laboratory studied the recrystallization of Tiagabine hydrochloride from ethyl acetate.

13. Our study indicated that Tiagabine hydrochloride has very poor solubility in ethyl acetate and requires more than 1000 volume. The small amount of Tiagabine hydrochloride obtained from the mother liquor appeared light brown in colour with bluish tinge. The large volume of ethyl acetate required for recrystallizing Tiagabine hydrochloride and the material obtained did not meet the basic requirement of appearance. Thus, our laboratory concluded that use of ethyl acetate as a recrystallization was not feasible. This is not surprising in view of the disclosure made in U.S. Patent 5,958,951 (cited by the Examiner), column 1, lines 39-49; and U.S. Patent 5,354,760 (of record), column 1, lines 46-48, where it is disclosed that use of ethyl acetate can give product with unwanted amounts of crystallizing solvent.

14. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, and any patent issuing thereon.

DATE: 25th February 2009 K. Srinivasu

K. Srinivasu, Ph.D.